REMARKS

Claims 10, 14-19 and 25-26 are currently pending in the application. Claims 16 and 26 are amended herein. No other claims have been amended.

SPECIFICATION

The Examiner has acknowledged the filed corrections to the specification concerning the name of the author from "Colowick et al" to "Wu and Grossman, Eds." As well as the incorporation of the year "1996" to the cited "White et al" article. Applicants gratefully acknowledge this action on the part of the Examiner.

INFORMATION DISCLOSURE STATEMENT

The Examiner has acknowledged the corrections made by the Applicant to incorporate the correct author from "Colowick et al" to "Wu and Grossman, Eds." and to include the year "1996" to the cited "White et al." reference. As the Information Disclosure Statement is a duplicate of the one sent December 13, 2004, Applicants acknowledge the Examiner's indication of the previously considered references as "duplicates" or "dup". Applicants gratefully acknowledge this action on the part of the Examiner.

The Examiner has indicated that the Information Disclosure Statement filed May 23, 2005 failed to comply with 37 CFR § 1.98 because a copy of the Hegenhart reference was missing and the Hegenhart and Myers et al. references were not in proper citation format. Applicant acknowledges that a copy of the Hegenhart reference was not received in connection with the May 23, 2005 filing of this Information Disclosure Statement. As Applicant respectfully explained in paragraph (a) of page 2 of the Supplemental Information Disclosure Statement filed May 23, 2005 (copy enclosed), they have been unable to locate a copy of the Hegenhart reference. Applicants have exhausted all possible resource options and continue to be unable to produce a copy of this reference.

Applicants respectfully request a suggestion from the Examiner with regard to how to deal with this issue.

With regard to the improper citation format of the Hegenhart and Myers et al. references, Applicants submit herewith a new PTO-Form 1449 which cite these references in the proper citation format. The Myers et al. citation now includes references to the appropriate volume and number of this reference. A copy of the Myers et al. reference is not included with this Reply as it was previously supplied to the Examiner with Applicant's May 23, 2005 filing. The Hegenhart citation is believed to be complete (i.e. the author, name of publication and date of publication are included). Applicant has also included the month of the publication (December) in the citation format for reference. As noted above, as well as on the enclosed PTO-Form 1449, Applicants are unable to locate a copy of the Hegenhart reference.

Applicants request that the information referred to in the present Reply and in the enclosed PTO-form 1449 now be considered. The filing of the enclosed PTO-form 1449 respectfully overcome the Examiner's objection to the Information Disclosure Statement.

WITHDRAWN REJECTIONS

The Examiner has withdrawn the prior rejection of claims 10 and 16-19 under 35 USC § 101. Applicants gratefully acknowledge these actions on the part of the Examiner.

The Examiner has withdrawn the prior rejection of claim 10 under 35 USC § 102(b). Applicants gratefully acknowledge this action on the part of the Examiner.

CLAIM REJECTIONS – 35 USC §112, FIRST PARAGRAPH

Claim 26

Claim 26 is newly rejected under 35 U.S.C. §112, first paragraph. The Examiner's contention is that the application as filed is not enabling for any second vector being "introduced to a non-human mammal." Respectfully, Applicant has further

amended claim 26 in an effort at clarifying the meaning and breadth of the claim. Applicant's reference was to the process of developing a transgenic animal carrying a DNA sequence of interest – here decorin. In that process, as is known in the art and as indicated in the specification, there is a process of amplifying a DNA sequence to aid in the efficiency of producing a series of transgenic cells in vitro. Once a DNA has been incorporated into the genome of the somatic cells of a target species the nuclei of those cells are used in nuclear transfer procedures. In the instant case such procedures require a significant amount of DNA of a specific sequence. This DNA is supplied by utilizing prokaryotes to produce it, followed by the use of restriction endonucleases to capture it. This process of prokaryote production of target DNA is old in the art. Reconsideration is respectfully requested.

Claims 10, 14-19, 25

Claims 10, 14-19 and 25 are rejected under 35 U.S.C. §112, first paragraph. The Examiner's contention is that the application as filed is not enabling for any organism other than the mammal species detailed in the specification – mouse. First, Applicants do thank the Examiner for indicating that the specification is in fact enabling for mouse. (Office Action of 10/20/2005, page 5). Applicants however, contend that the instant specification is enabling with regard to broader spectrum of mammalian species. Applicants point out that the Examiner has agreed that the transgenic mouse carrying a human DNA sequence that is expressed through the activation of a goat promoter sequence is enabled. Functionally then, how different would the specification have been if the human protein secreted had been collected from a transgenic goat as the result of the action of a mouse promoter turned on during normal lactation? The point is that Applicants have utilized a known "tool box" of molecular tools to produce a recombinant human protein of unique identity in a "bench top" mammalian species. The novelty lies in the protein produced – its sequence and production within a transgenic mammalian platform under the control of normal mammalian lactation hormones.

Reconsideration is respectfully requested.

As previously stated, the essential novelty of the patent lies in the manipulation and engineering of the decorin molecule itself within the transgenic mammalian platform,

and its physiological activity therein. The fact that the prior art did not contemplate the generation and use a transgenic animal for the production of recombinant decorin is the precise reason why the current application is patentable -- it is novel.

More to the point, the CAFC has continued to apply the rule that disclosure of a species is sufficient written description support for a later claimed genus including that species. . . . If the difference between members of the group is such that the person skilled in the art would readily discern that other members of the genus would perform similarly to the disclosed members. Bilstad v. Wakalopulos (Fed. Cir. 2004). For the purposes of the instant application, Applicants maintain that the utilization of mice as an experimental platform has long been accepted in the art as a "bench top" experimental animal whose utility is found in the substantial likelihood that other members of the genus would perform similarly, thereby enabling their use with the current invention as well.

Respectfully, it must be remembered, that to be enabling, the specification of a patent application need only teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. Genentech v. Novo Nordisk, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997). This has been done in the instant specification. Moreover, as here, the "conception of a species within a genus may constitute conception of the genus," Oka v. Youssefyeh, 849 F.2d581, 583 (Fed. Cir. 1988).

Essentially, patent law and, in particular, the law relating to biotechnology inventions, has never required that an applicant make and test every member of a large genus to obtain comprehensive claims. Rather, to enable a genus, the patent specification need only teach the skilled worker how to make and use species commensurate in scope with the genus through no more than routine experimentation. In re Angstadt, 537 F.2d 498 (C.C.P.A. 1976). In the instant case the "prototype" organism was the mouse.

The mice used for the experiments that led to the current invention were bred for the purpose of scientific experimentation precisely because the results achieved with them can be and in practice ARE "scaled-up" to a "production volume" bioreactor – a larger mammal. This is the only way to make the transgenic animal biopharmaceutical production business possible.

The current Assignee is a transgenic company that does not use stainless steel bioreactors of various sizes – one useful at the benchtop and another, larger, stainless steel reactor useful for commercial production. Rather, the instant Assignee utilizes mammals of varying milk "production capacities" and breeding rates for differing proteins. In this process mice are used as proof of concept animals. If the techniques used therein for a specific endeavor are successful – here recombinant decorin production with a specific DNA sequence and promoter – that same "package" will be used in larger animals – aka – "bigger bioreactors" because success of the DNA sequence and protein production at a viable rate have already been determined.

Moreover, in determining whether the disclosure requirement is satisfied, the person(s) *skilled* in the art are *presumed* to be aware of all of the relevant literature, including trade publications, textbooks, technical journals, and contemporary U.S. patents. Whereupon the disclosure of a relevant discovery, and subsequent allowance, as a patent would then provide a variety of potential uses for those skilled in the art, as mentioned above. With regard to the existing milieu of prior art, Applicant points to recently issued patents below that were granted broader claims for the genus or a Markush group of animals when the specifications only presented a single animal – typically a mouse.

United States Patent 7,030,289 Cottingham et al. Issued: April 18, 2006
Specification describes only: Sheep
Claims include: sheep, cow, goat, rabbit, mouse, camel, water-buffalo, pig or horse.

United States Patent 6,987,211 Soreq et al. Issued: January 17, 2006
Specification describes only: Mice
Claims include: mouse, goat, cow or pig.

United States Patent 6,743,966* Smith et al. Issued: June 1, 2004
Specification describes only: Mice
Claims include: mouse, rabbit, goat, cow or pig.
[*NOTE: This patent is exclusively licensed by the instant Assignee]

The point for presenting the above is that it is not and should not be fatal to claim a genus if the operative species is one that is known in the art to be a foundational or

"benchtop" production vehicle (e.g., mice). See. In re Angstadt, 537 F.2d at 502-03. In a sense, it is true that the result of an enablement inquiry cannot be predicted with certainty. Enablement under 35 U.S.C. § 112 is a question of law which takes into account a number of factual determinations, including those defined by scientific principles laid out in the prior art. See, In re Wands, 858 F.2d at 736-37; M.P.E.P. § 2164. Here, those considerations underscore the enablement of the genus mammals through the use of a prototype species. Reconsideration is requested.

CLAIM REJECTIONS UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claim 26 stands rejected under 35 U.S.C. §112, second paragraph for being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. This rejection is respectfully traversed. The reasons for potential confusion relative to this claim were discussed above. The rejection enunciated by the Examiner under 35 U.S.C. §112, second paragraph has been addressed through specific amendment to the claim. As previously stated, the amendment was made to clarify, particularly point out, and distinctly claim the subject matter of the invention along the guidelines of what the Examiner noted as enabled in the last Action. Reconsideration of the rejection of amended claim 26 under 35 U.S.C. § 112, second paragraph, is respectfully requested.

CLAIM REJECTIONS – 35 USC §102

Claim 19

Claims 19 stands rejected under 35 USC § 102 as being anticipated by Hering et al. Respectfully, with the previous amendment of claim 19 to narrower subject matter this new rejection is traversed.

As noted, anticipation requires **both an identity of elements and identity of process.** This Hering et al., simply does not provide. Tyler Refrigeration v. Kysor Indus. Corp., 777 F.2d 687, 227 U.S.P.Q.177 (Fed Cir. 1986). Respectfully, the Hering reference does not "inherently" or even inferentially disclose the instant invention, or read on any of its amended claims. Moreover, to anticipate a claim, a prior art reference

must disclose every limitation of the claimed invention, either explicitly or inherently. Mehl/Biophile Int'l Corp. v. Milgraum, 192 F.3d 1362; 52 U.S.P.Q.2D 1303 (1999). This Hering does not do. In fact, Applicant points to the Examiner's own discussion of Hering in that Hering et al., teaches the production of "bovine decorin", not human decorin in "bacterial cells" not the mammary gland of a whole animal (page 14 10/20/2005 Office Action). The scientific tools needed to generate an in vitro colony of prokaryotes as opposed to the production of a sexually mature transgenic mammal are VASTLY different. Respectfully, this alone should disqualify Hering et al., from even remotely entering the realm of anticipatory prior art.

Relative to the MPEP, however, in order to avoid rejection for anticipation, it is only necessary to show that claim 19 contains at least one element not disclosed in Hering et al. More specifically, claim 19 recites (including limitations from its supravening base claim) several elements not present or suggested in any of the teachings of Hering et al., including:

a) Non-human transgenic mammals – not prokaryotes, not in vitro

b) Recombinant human decorin – not bovine decorin with a variant amino acid structure and sequence;

and,

c) production in milk – an impossibility with a single-celled organism

None of the elements a-c above are disclosed in the Hering et al., reference. Therefore, it is respectfully proposed that the rejection of claim 19 for anticipation by the Hering et al., reference is overcome and cannot be maintained. Reconsideration of the rejection of claim 19 under 35 U.S.C. § 102, is requested.

CLAIM REJECTIONS – 35 USC §103

Houdebine et al., Krusius et al., Ruoslahti et al., Mann et al., and Roberts et al.,

Claims 10, 14, 16-19 and 25 are rejected under 35 U.S.C §103(a) as being

unpatentable over Houdebine et al., in view of Krusius et al., Ruoslahti et al., Mann et al., and Roberts et al. Previously independent claims 10 and 18 were amended to comply with the Examiner's concerns. Applicants again point to those amendments to the independent claims in response to the Examiner's rejections. Base claim 10's amendments limitations on breadth take it well outside any anticipation or obviousness rejection based on the Houdebine citation or other references provided by the Examiner. Applicant requests reconsideration.

At the outset it should be stated that Applicants purposefully employed a secretion system of incredible power and complexity (mammary epithelial cell lactation) that provides for the production and secretion of specific hormonally induced proteins (e.g., milk and milk proteins) in incredibly high concentration and pushes them out of the system of a whole animal in a regular reliable amount. In this way transgenic animals are quite unlike any other tool in the molecular biologists proverbial "tool kit." This is not a slightly changed in vitro system. It is not similar to prokaryotic production of proteins in stainless steel vats or even mammalian cell production in bioreactors. This is the use of whole animals and organ systems to produce proteins in better quantity and enhanced complexity. Given this, and the production of human decorin, much of the cited prior art falls away.

As presented above, neither Houdebine et al., nor Ruoslahti – or the other cited references provide sufficient guidance along this line to negative patentability. Applicant focused on these citations as the most relevant art because the techniques and the authors are well known in the field. If these citations are taken out of the mix of the cited prior art the prima facie case of the Examiner, respectfully, cannot stand.

Ruoslahti

As previously stated, Ruoslahti et al., relates to the use of cell culture *in vitro* techniques to produce decorin. However, these citations ignore the activities of those skilled in the art at the time of this invention. More to the point, Ruoslahti *et al.*, do not disclose and is simply SILENT with regard to any meaningful instruction with regard to the techniques needed or problems associated with the inclusion of any nucleic acid

construct in the cells of a host transgenic mammal leading to the expression of a biologically active construct. The citations also fail to mention any teaching with regard to the expression or recovery of proteins from the milk of transgenic mammals.

Instead, Ruoslahti *et al.*, provides a primer on the use of decorin exemplified exclusively through production through *in vitro* methods. In this light the citations are simply incapable of supporting the rejection of the instant claims. Reconsideration is requested.

As stated previously, the Examiner's analysis inappropriately bases its rejection on the use of Ruoslahti *et al.*, on the premise that one expression system and all of the interplay in the various tools used to achieve expression of a target protein or protein fragment is like another, and that therefore any cellular expression system with any given target protein for any biologically active molecule is an appropriate and analogous prior art reference for the claimed invention of another such expression system. This is simply not the case. The invention of the Appellants required a systematic understanding of the host of problems seen before in the prior art and a novel way of using a variety of complex tools to produce the raw material for a new class of molecule produced in a novel way. Something which quite simply had not been done before, or reduced to practice with regard to the decorin molecule. Ruoslahti, does not approach explaining a whole animal transgenic production platform.

Similarly, Houdebine cannot negative the current claims, as he does not produce, theorize or indicate in any affirmative manner the production of human decorin.

Reconsideration of the rejection of amended claims under 35 U.S.C. § 103(a) is respectfully requested.

No fee other than that for the 3 month extension of time is deemed necessary in connection with the filing of this Reply and Amendment. However, the Commissioner is authorized to apply any fee which may now be or hereafter be due for this application to Deposit Account No. 502092.

Early and favorable action is earnestly solicited.

Respectfully submitted,

Date: 4/20/2006

By: _____

Byron V. Olsen, Reg. No. 42,960
ATTORNEY FOR APPLICANT
GTC Biotherapeutics, Inc.
175 Crossing Blvd., Suite 410
Framingham, MA 01702
Tel. # (508) 370-5150
Fax # (508) 370-3797